

## PATENT

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:

SKOULTCHI

Serial No.: 08/102,390

Group Art Unit: 1804

Filed: August 5, 1993

Examiner: Ziska, S.

For: PRODUCTION OF PROTEINS  
USING HOMOLOGOUS  
RECOMBINATIONAtty Docket No.:  
7639-017/Cell 3.2PETITION TO MAKE SPECIAL PURSUANT  
TO 37 C.F.R. § 1.102(d)Honorable Commissioner of Patents and Trademarks  
Washington, D.C. 20231

Sir:

Applicant petitions pursuant to 37 C.F.R. §1.102(d)  
to make the above-identified application special.

This application should be made special because the  
invention disclosed therein relates to the safety of research  
in the field of recombinant DNA (37 C.F.R. § 1.102(d), also  
see Manual of Patent Examining Procedure ("MPEP") §708.02  
VII). If this Petition is not granted on the grounds that the  
invention relates to the safety of research in the field of  
recombinant DNA, Applicant alternatively petitions that the  
application be made special on the grounds of on-going actual

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office  
on the date shown below.

Alan L. Koller 37.371  
Alan L. Koller (Reg. No.)

Date: December 29, 1994

infringement of some of the claims of the application (37 C.F.R. §1.102(d), also see MPEP, §708.02 II).

This Petition is accompanied by a Petition Fee Transmittal Sheet authorizing payment of the appropriate fee as set forth in 37 C.F.R. §1.17(i).

**I. BACKGROUND**

The above-captioned application is a Rule 60 continuation application of U.S. Serial No. 787,390, filed November 4, 1991, now abandoned, which is a continuation-in-part of application U.S. Serial No. 432,069, filed November 6, 1989, now abandoned.

**II. THE APPLICATION SHOULD BE MADE SPECIAL BECAUSE IT RELATES TO THE SAFETY OF RESEARCH IN THE FIELD OF RECOMBINANT DNA**

As demonstrated by the Declaration of Daniel J. Capon (the "Capon Declaration") submitted concurrently herewith, the present invention relates to the safety of research in the field of recombinant DNA by providing methods and compositions for transferring different nucleotide regulatory sequences into mammalian host cells to control endogenous gene expression without requiring the use of viral or retroviral vectors, and in a precisely targeted manner. Accordingly, this application should be made special.

Concern has been expressed by some parties that use of bioengineered viral or retroviral vectors to transfer nucleotide sequences into mammalian cells carries with it

certain risks. See, for example, ¶ 4 of the Capon Declaration citing such concerns in PCT International Publication WO 94/12650, pertinent pages of which are attached thereto as Exhibit A.

Applicant's invention reduces or eliminates these risks for both researchers in this particular field of recombinant DNA research and recipients of gene therapy by providing for the transfer of nucleotide sequences into mammalian host cells without using viral or retroviral vectors [Capon Declaration, ¶ 6]. For example, the specification, on page 9, line 35 to page 10, line 4, states:

In carrying out the homologous recombination, the DNA will be introduced into the primary cells. Techniques which may be used include calcium phosphate/DNA co-precipitates, microinjection of DNA into the nucleus, electroporation, bacterial protoplast fusion with intact cells, transfection, polycations, e.g., polybrene, polyornithine, etc., or the like. The DNA may be single or double stranded DNA, linear or circular.

Targeting vectors which are useful in practicing Applicant's invention may thus comprise naked strands of DNA which can be directly introduced into mammalian host cells.

Additionally, Applicant's invention reduces or eliminates these risks by providing for the transfer of nucleotide sequences into mammalian host cells in a precisely targeted fashion, thereby reducing or eliminating the possibility of multiple integrations at random sites in the mammalian host cell genome [Capon Declaration, ¶ 7].

Accordingly, because Applicant's invention increases the safety of recombinant DNA research, this application should be made special.

Petitioner submits that generally accepted safety procedures for manipulating recombinant DNA molecules and organisms transfected with recombinant DNA molecules are being followed in all experimentation carried out by Applicant or Petitioner in this field.

**III. THIS APPLICATION SHOULD BE MADE  
SPECIAL BECAUSE OF ACTUAL  
INFRINGEMENT OF ITS CLAIMS**

As demonstrated by the Declaration of Laura A. Coruzzi (the "Coruzzi Declaration") submitted concurrently herewith, there is on-going "actual infringement" of some of the claims of the above-identified application as amended in an Amendment Under 37 C.F.R. §1.115, filed June 1, 1994. Accordingly, this application should be made special.

Transkaryotic Therapies, Inc. ("TKT") is currently making products and using methods for gene therapy which are covered by amended claims 26 and 48, respectively, of the above-identified patent application [Coruzzi Declaration, ¶¶ 4 and 5; Capon Declaration, ¶¶ 10 and 11, and Exhibits B-D attached thereto]. Cell Genesys, Inc. ("Cell Genesys"), the assignee of this patent application, first became aware of the use of such methods on or about January 12, 1994 [Capon Declaration, ¶ 9].

TKT's gene activation technology is described in Exhibits B-D attached to the Capon Declaration. Exhibit B comprises pertinent pages from TKT's S-1 Registration Statement, as filed with the Securities and Exchange Commission on July 26, 1993. Exhibit C is a published report entitled "TKT Scientists Deliver Erythropoietin (EPO) By Gene Therapy; Novel Gene Activation Technology Eliminates Need For EPO License" which appeared in PR Newswire's "Today's Headlines" on January 12, 1994. Exhibit D is a published report entitled "Mice Produce EPO In Gene Therapy Study" which appeared in BioWorld Today, Vol.5, No. 9, pp. 1-2, on January 13, 1994.

Exhibit B, page 4, second paragraph, states:

TKT has developed proprietary gene targeting and gene isolation technologies to enhance its gene therapy products. Gene targeting is a technique in which genes are inserted or replaced at a chosen site on a given chromosome (emphasis added).

From this statement, TKT's gene activation technology appears to provide a method for precisely targeted insertion of different nucleotide sequences into a chromosome [Capon Declaration, ¶ 10(a)].

Exhibit B, page 22, fifth full paragraph, further states:

Gene targeting is based on a naturally occurring process called 'homologous recombination,' in which a DNA sequence on one chromosome switches locations with a similar DNA sequence on another chromosome. The Company's gene targeting technology is based on attaching a tag to the gene which guides it to the desired location on the target chromosome where homologous recombination occurs.

resulting in incorporation of the new gene.  
TKT's gene targeting technology potentially  
could increase levels of gene expression ...  
(emphasis added).

Thus, TKT's gene activation technology utilizes homologous recombination to insert a different nucleotide sequence into a chromosome, in which the "tag" which guides a gene to a desired location on the target chromosome is apparently a nucleotide sequence that is homologous to a target sequence in the host cell genome where insertion of the gene is desired [Capon Declaration, ¶ 10(b)].

Exhibit B, page 21, middle of fifth full paragraph, further states:

In order to obtain expression of the therapeutic protein, a synthetic fusion of the promoter and structural regions must be precisely engineered using molecular biological techniques. TKT has successfully created such 'fusion genes' and has used them to accomplish the expression in fibroblasts of a variety of human proteins, including growth hormone, EPO, Factor VIII, Factor IX, insulin and the LDL receptor. Having established this ability to express proteins in transfected human fibroblasts, the Company has focused on improving their expression (emphasis added).

From this statement, TKT appears to have used its gene activation technology to produce and express "fusion genes", i.e., nucleotide sequences in which different regulatory elements are combined with endogenous genes encoding proteins such as human EPO, human Factor VIII, etc., in mammalian host cells, in this case, human fibroblast cells [Capon Declaration, ¶ 10(c)].

Exhibit C, fourth paragraph, states:

TKT's proprietary gene activation technology involves the surgically precise modification of a patient's cells. A piece of DNA is inserted adjacent to the natural EPO gene in normal cells -- this piece of DNA represents a genetic 'switch' that turns on EPO production in the cells. The technology is an extension of the work on the genetic modification of normal human cells developed at TKT over the past five years. The technology can be applied to the activation of essentially any human gene, the company noted (emphasis added).

Furthermore, Exhibit D, page 2, first full paragraph, states:

[TKT's President and Chief Executive Officer, Michael Forrest], explained that within the skin fibroblast cell there is a control region - a gene sequence - that tells the cell not to make EPO since EPO is not naturally produced in skin fibroblast cells. He said TKT is able to insert its own control region in the cell that deletes the existing control region. The new control region instructs the cell to produce EPO (emphasis added).

From these two statements, TKT's gene activation technology appears to involve the replacement of a wild-type (endogenous) nucleotide regulatory element, i.e., the "genetic switch" or "control region" described above, that is normally associated with an endogenous gene, with a different nucleotide regulatory element that activates gene expression. The insertion of the different nucleotide regulatory element "adjacent" to the natural gene indicates that this regulatory element is inserted so that it is operatively associated with the endogenous gene of the mammalian host cell. That "this piece of DNA ... turns on EPO [protein] production in the cells" indicates that expression of the endogenous gene is

controlled by the inserted different regulatory element [Capon Declaration, ¶ 10(d), (e)].

Exhibit B, page 21, sixth paragraph, states:

Following transfection, a single cell selected from a pool of transfected cells is cloned (i.e., copied) and propagated, resulting in a uniform population of identical cells for implantation. ... [T]he Company clones a cell that is capable of producing the therapeutic protein at desired levels (emphasis added).

Thus, following transfection, mammalian host cells in which there has been successful integration of the different nucleotide regulatory sequence so that it is operatively associated with, and controls expression of, the endogenous gene, are selected [Capon Declaration, ¶ 10(f)].

Exhibit C, fifth paragraph, states:

TKT is currently engaged in pre-clinical studies of the company's EPO gene activation product for the treatment of severe anemia and is discussing additional gene activation targets with corporate partners (emphasis added).

Finally, Exhibit D, page 1, first paragraph, states:

Mice that received implants of skin cells modified to contain the erythropoietin gene have produced therapeutic levels of EPO for one year, Transkaryotic Therapies Inc. reported ... (emphasis added).

From these two statements, it appears that TKT is presently using its gene activation technology to produce proteins in mammalian host cells [Capon Declaration, ¶ 10(g), (h)].

On the basis of the above-cited description, it is plain that TKT's gene activation technology produces a mammalian host cell, and is a method for producing proteins in

a mammalian host cell, in which expression of an endogenous gene in the mammalian host cell is altered, i.e., activated, by replacing a wild-type nucleotide regulatory element in the host cell with a different nucleotide regulatory element via homologous recombination.

It is also plain that the different regulatory element is integrated into the mammalian host cell genome so as to be operatively associated with the endogenous gene of the mammalian host cell, that expression of the endogenous gene is controlled by the integrated different regulatory element, and that altered mammalian host cells with the correctly integrated different nucleotide regulatory element are selected and propagated [Capon Declaration, ¶ 11].

Applicant's Attorney has also made a "rigid comparison" of TKT's gene activation technology with amended claims 26 and 48 of this application, using the descriptions of TKT's gene activation technology presented in Exhibits B-D of the Capon Declaration and Dr. Capon's opinion of what those descriptions mean [Capon Declaration, ¶¶ 10 and 11]. On the basis of that comparison, Applicant's Attorney believes that some of the amended claims of this application (claims 26 and 48) are "unquestionably" infringed by TKT's use of its gene activation technology [Coruzzi Declaration, ¶¶ 4, 5].

Applicant's Attorney has made a "comparison" with respect to amended claim 26,<sup>1/</sup> and believes that TKT's gene

---

<sup>1/</sup> Claim 26, as presently amended, recites:

(continued...)

activation technology "unquestionably" infringes such claim because TKT's use of its gene activation technology is producing mammalian host cells having a modified endogenous gene comprising a nucleotide regulatory element different from the wild-type regulatory element normally associated with the endogenous gene, in which:

a) the different regulatory element is integrated into the genome of the mammalian host cell via homologous recombination;

b) the integrated regulatory element is operatively associated with the endogenous gene of the mammalian host cell; and

c) expression of the endogenous gene is controlled by the integrated regulatory element [Coruzzi Declaration, ¶ 4]

Applicant's Attorney has also made a "comparison" with respect to amended claim 48,<sup>2/</sup> and believes that TKT's

<sup>1/</sup> (...continued)

A mammalian host cell having a modified endogenous gene comprising a nucleotide regulatory element different from the wild-type regulatory element normally associated with the endogenous gene integrated, via homologous recombination, into the genome of the mammalian host cell, so that the integrated regulatory element is operatively associated with the endogenous gene of the mammalian host cell and expression of the endogenous gene is controlled by the integrated regulatory element.

<sup>2/</sup> Claim 48, as currently amended, recites:

A method for producing a mammalian host cell having a modified gene, comprising:

(a) transforming a mammalian host cell with a nucleotide sequence comprising a nucleotide regulatory element flanked by a nucleotide sequence

(continued...)

gene activation technology "unquestionably" infringes such claim because TKT's gene activation technology is a method for producing a mammalian host cell having a modified gene, comprising:

a) transforming a mammalian host cell with a nucleotide sequence comprising a nucleotide regulatory element flanked by a nucleotide sequence homologous to a region of the host cell genome within or proximal to an endogenous gene present in the mammalian host cell so that the nucleotide regulatory element is integrated via homologous recombination into the genome of the mammalian host cell; and

b) selecting a transformed mammalian host cell having the modified gene in which the integrated nucleotide regulatory element is operatively associated with the endogenous gene so that expression of the endogenous gene is controlled by the integrated regulatory element [Coruzzi Declaration, ¶ 5].

Applicant's Attorney has a "good knowledge of the pertinent prior art" and believes that all of the claims in the application are allowable [Coruzzi Declaration, ¶ 6]. The

---

2/ (...continued)

homologous to a region of the host cell genome within or proximal to an endogenous gene present in the mammalian host cell so that the nucleotide regulatory element is integrated via homologous recombination into the genome of the mammalian host cell; and

(b) selecting a transformed mammalian host cell having the modified gene in which the integrated nucleotide regulatory element is operatively associated with the endogenous gene so that expression of the endogenous gene is controlled by the integrated regulatory element.

Examiner in charge of Applicant's application cited several documents during her examination (see, for example, Paper No. 11, mailed September 21, 1994). Applicant also submitted an Information Disclosure Statement Under 37 C.F.R. §1.56 on November 9, 1993, and a Supplemental Information Disclosure Statement on June 1, 1994.

Applicant's Attorney has reviewed all of these documents and believes that all of the amended claims now pending in this application are allowable and patentable over them [Coruzzi Declaration, ¶ 6].

#### IV. CONCLUSION

This application should be made special because it relates to the safety of research in the field of recombinant DNA. In the alternative, this application should be made special because there is on-going actual infringement of the claims as currently amended.

Applicant requests that the Patent and Trademark Office grant this Petition and make this application special.

Respectfully submitted,

Date: 12/29/94

By Samuel B. Adams 30,605  
Laura A. Coruzzi 30,742  
Laura A. Coruzzi (Reg. No.)

ATTORNEY FOR APPLICANT

PENNIE & EDMONDS  
1155 Avenue of the Americas  
New York, New York 10036  
(212) 790-9090